

Exhibit 36

Summary Minutes - December 13-15, 2000

NTP Board of Scientific Counselors Report on Carcinogens Subcommittee

**SUMMARY MINUTES
of the
National Toxicology Program
Board of Scientific Counselors
Report on Carcinogens Subcommittee Meeting**

December 13 - 15, 2000

TABLE OF CONTENTS

I.	Introduction and Background	1
II.	Peer Review of Substances Nominated for Listing in the Tenth Report on Carcinogens	1
	• Broad Spectrum Ultraviolet (UV) Radiation and UVA, and UVB, and UVC	1
	• Trichloroethylene.....	4
	• Methyleugenol	7
	• Metallic Nickel and Nickel Alloys	8
	• Chloramphenicol.....	11
	• Talc (Asbestiform and Non-asbestiform)	12
	• Estrogens.....	18
	• Wood Dust	19

Attachments

1. Federal Register Announcement
2. Agenda and Roster of Subcommittee Members

Summary Minutes - December 13-15, 2000

NTP Board of Scientific Counselors Report on Carcinogens Subcommittee

The National Toxicology Program (NTP) Board of Scientific Counselors Report on Carcinogens (RoC) Subcommittee (the Subcommittee) held its sixth meeting on December 13, 14, and 15, 2000 at the Wyndham City Center, 1143 New Hampshire Avenue, NW, Washington, D.C. (**Attachment 1: *Federal Register* meeting announcement**; **Attachment 2: *Agenda and Roster of Members***.) Members of the Subcommittee present were: Drs. Clay Frederick (Chairperson), George Bonney, Hillary Carpenter, Yvonne Dragan, John Froines, Karl Kelsey, Michele Medinsky, Rafael Moure-Eraso, Jill Pelling, Allan Smith, and Shelia Zahm. Expert Consultants to the Subcommittee are Drs. David Phillips and Hiroshi Yamasaki. Members not present were Drs. Stephen Hecht and Walter Piegorsch.

I. Introduction and Background: Dr. Christopher Portier, Acting Director, Environmental Toxicology Program (ETP), National Institute of Environmental Health Sciences (NIEHS), welcomed Subcommittee members and members of the public in attendance. Dr. Portier noted that the nominations being reviewed during this meeting were the second group of nominations to be considered for the 10th *Report on Carcinogens*, and reported that the 9th *Report* was released in May 2000. He briefly reviewed the composition of the NTP and gave a brief background on the *Report on Carcinogens* (RoC). In 1996, to involve greater outside scientific input and to provide the opportunity for greater public comment into the review of nominations, the RoC Subcommittee was created. Dr. Portier said that the reviews at this meeting allow for a public evaluation following earlier reviews by two Federal scientific review groups, the NIEHS Review Committee for the Report on Carcinogens (RG1) and the NTP Executive Committee Interagency Working Group for the Report on Carcinogens (RG2). Following the Subcommittee meeting, there will be a public comment period for the recommendations from all three committees, followed by a review by the NTP Executive Committee. The Executive Committee recommendations along with those of the three scientific review groups are forwarded to the Director, NTP, who then decides what will be included in the draft of the 10th RoC that will be forwarded to the Secretary of Health and Human Services. Dr. Portier concluded by emphasizing that this is a hazard identification process and not a risk assessment process, and that the role of the Subcommittee is strictly advisory to the NTP. He said that because of the large number of requests for time, public commentators would be limited to seven minutes.

Dr. Frederick reiterated that the Subcommittee's role is advisory and its review is focused on hazard identification. Further, consensus is not sought within the group, and a divergence of opinion can provide valuable information to the Program. Dr. Frederick went over the review format to be used with each nomination. The basis for each nomination will be presented by an NTP scientist who will discuss the nomination, including data relating to human cancer, animal cancer, mechanistic information, and summaries of the arguments for or against listing and will provide the recommendations, including the votes, of the two Federal review committees, RG1 and RG2. Following the staff presentation, Subcommittee members will be allowed to ask clarifying questions. Members of the public then will be invited to make their comments. The members of the Subcommittee who have primary review responsibilities for the nomination will then present their evaluations. This will be followed by further discussion among the Subcommittee members concluding with motions and votes on recommendations to be forwarded to the NTP.

II. Peer Review of Substances Nominated for Listing in the 10th *Report on Carcinogens*:

Broad Spectrum Ultraviolet (UV) Radiation and UVA, and UVB, and UVC -- Dr. Ruth Lunn, NIEHS, presented the nomination and said that broad spectrum UV radiation and UVA, UVB, and UVC were recommended by RG2 for listing in the 10th *Report* based on the NTP's previous review of solar radiation and exposure to sunlamps or sunbeds. Solar radiation and exposure to sunlamps or sunbeds are listed as *known to be human carcinogens* in the 9th *Report on Carcinogens*. Further, UVA, UVB, and UVC were characterized by the International Agency for Research on Cancer (IARC) in 1992 as probably carcinogenic in humans (Group 2A). Humans can be exposed to UV radiation (UVR) from natural or

Summary Minutes - December 13-15, 2000

NTP Board of Scientific Counselors Report on Carcinogens Subcommittee

artificial sources with the predominant exposure being solar radiation. The levels of UVA and UVB exposure from natural sources vary with latitude, altitude, time of day and season. Human epidemiological studies on UVR come from studies on solar radiation and exposure to artificial sources. Dr. Lunn said numerous epidemiological studies have demonstrated a causal relationship between exposure to the sun and skin cancer both melanoma and non-melanoma. She said that intermittent sun exposure appears to be more important for the development of malignant melanoma, whereas chronic sun exposure may be more important for development of squamous cell carcinoma. Evidence that the UVR component is the carcinogenic component of solar radiation comes from human epidemiological and mechanistic and animal studies using artificial sources of UVR. The majority of the epidemiologic literature on UV radiation from artificial sources derives from studies on exposure to sunlamps and sunbeds with studies grouped into four tiers based on quality of information. For studies in the tier having the best information, a positive association was observed in five of six studies with odds ratios from 1.1 to 2.6, while exposure/response relationships were observed in four out of five studies. UVR and its components all produced skin tumors in experimental animals, are mutagenic in bacteria and mammalian cells, and are positive in human *in vivo* and *in vitro* studies. UVA is poorly absorbed by DNA and induces DNA damage indirectly via reactive oxygen species, while UVB and UVC are absorbed and produce DNA damage primarily through 6-4 photoproducts and cyclobutane pyrimidine dimers, both types of exposure leading to skin cancer in humans. Dr. Lunn reported that for broad spectrum UVR, there was sufficient evidence of carcinogenicity from studies in humans supported by evidence in animals while for the individual components there is limited evidence in humans because epidemiological studies are not able to assess the individual components of UVR, although for UVA and UVB, there is strong evidence from human mechanistic studies. Both RG1 (six votes) and RG2 (eight votes) unanimously recommended that UVR be listed as *known to be a human carcinogen*, and that UVA, UVB, and UVC each be listed in the 10th Report as *reasonably anticipated to be a human carcinogen*.

Public Comments: Mr. Donald Smith, Executive Director, North American Alliance of Tanning Salon Owners, stated that there should be a clear and conspicuous statement of the limitations of the RoC on the first page of copies of the Draft Background Document (DBD) yet to be distributed for the current nomination, on the first page of copies of the 9th Report yet to be distributed, and on the first page of the forthcoming 10th Report. These limitations mainly pertain to providing information on the beneficial effects of UVR. He said this statement should indicate that the RoC does not present a quantitative risk assessment of carcinogenic risk of any “agent, substance, or mixture.” Further, such formal risk assessments are beyond the scope of the document. Mr. Smith further stated that if the proposed listing is approved there should be a detailed explanation of the fact that UVR exposure is needed for conversion of vitamin D in the body and why underexposure to UVR creates hazards to human health.

Mr. Stephen Ross of Akin, Gump, Strauss, Hauer, and Feld and representing the Indoor Tanning Association, said there are questions as to the science supporting the nomination and questions with regard to interpretation. He complained that there was insufficient notice given of the process to the Association and the industry that it represents such that the industry did not have proper opportunity to present information in response.

Mr. Jerry Deveney, Sun Ergoline, Inc., commented that the information, data, testing procedures and conclusions used to support the nomination of broad spectrum UVR for listing as a known carcinogen appear limited in scope with respect to inclusion of important variables that could potentially influence outcomes and determinations. Further, he said that one would think it prudent that before listing a substance essential for human life as a known carcinogen, equal effort should be exercised into understanding potential effects from non-exposure. He concluded that listing broad band UVR, without a benefit disclaimer, could have a devastating economic impact on major U.S. corporations.

Summary Minutes - December 13-15, 2000

NTP Board of Scientific Counselors Report on Carcinogens Subcommittee

Mr. Robert Wagner, AEGIS Inc., stated that data used to establish conclusions on sunlamps was (1) gleaned not from direct or supported testing but rather from a group of existing papers, and (2) no other research from FDA or translated foreign studies was taken into consideration. He noted that all testing reported was conducted on mouse skin, a medium which is attached to a nocturnal animal that has evolved in environments with little or no exposure to sunlight, and is predisposed to compound immunodeficiencies. Mr. Wagner said that AEGIS believes that NIEHS should reevaluate its earlier listing of sunlamps, and contract or perform its own studies on the effects of broad-based UV on humans prior to release of the 10th RoC.

Primary Reviews: Dr. Allan Smith, a primary reviewer, said he could support classification of UVR as *known to be a human carcinogen* while he thought UVA, UVB, and UVC could be *reasonably anticipated to be human carcinogens*. He based his conclusions primarily on three large published epidemiological studies. Dr. Smith said the primary concern he had with the findings were with the probable confounding effects of recreational sun exposure on cases where excesses of skin cancer could be attributed to sunlamp or sunbed use, especially in that users of sunlamps were considered more likely to have sun exposure. The only major U.S. study of sunlamps found the odds ratio reduced from 1.3 to 1.1 after adjusting for recreational sun use. Dr. Smith stated he was perplexed by the most recent report, a Swedish study (Westerdahl *et al.*, 2000), where an already high odds ratio (4.2) went up (8.1) when adjusted for other variables and he attributed this to imprecision resulting from very high UVR exposure for controls as well.

Dr. Pelling, also a primary reviewer, agreed that broad spectrum UV radiation should be listed as *known to be a human carcinogen* based on a large body of epidemiological evidence indicating exposure to UVR causes an increased risk of developing squamous cell and basal cell carcinomas and both cutaneous and uveal melanomas. She noted that broad spectrum UV is not defined specifically in the DBD, but it inferred that the definition is radiation between 100 and 400 nanometers (nm). Dr. Jameson agreed and said this would be clarified in the document. Dr. Pelling commented that the evidence from human studies attributing skin carcinogenicity to exposure to the various “windows” of UVR is limited, and therefore, UVA, UVB, and UVC should be listed as *reasonably anticipated to be human carcinogens*.

Dr. Yamasaki, also a primary reviewer, agreed with the proposed listings for UVR, as *known to be a human carcinogen*, and for UVA and UVC as *reasonably anticipated to be human carcinogens*. He agreed that it is not possible to differentiate each UVR component in epidemiological studies; however, he maintained it was possible to do so through animal studies as well as mechanistic approaches. Dr. Yamasaki reported that UVB is known to induce skin tumors on mouse skin and on human skin grafted to the back of SCID mice. UVB-induced mouse skin tumors contained p53 mutations with particular sequences that are also associated with human non-melanocytic skin cancers. He said that these data, along with epidemiological data, are compelling enough to consider UVB as *known to be a human carcinogen*. Dr. Smith inquired as to whether this particular mutation is found in skin tumors from parts of the body where there is not likely to be sun exposure. Dr. Yamasaki said that it is very hard to find skin tumors not related to solar radiation. Dr. Pelling noted from her review of the recent literature that nearly 90% of human squamous cell tumors contain some sort of p53 mutation.

In further discussion, Dr. Medinsky, noting comments by a public speaker, urged more prominent mention of the beneficial role of UVR as well as the Vitamin D issue. Further, the fact that these are hazard identification and not risk assessment documents should be emphasized. Dr. Frederick agreed alluding to a similar discussion in the review of tamoxifen for the 9th RoC.

Dr. Frederick announced that there would be separate motions and discussion for UVR and each of its components. Dr. Smith moved that broad spectrum UVR be recommended for listing in the 10th RoC as *known to be a human carcinogen*. Dr. Pelling seconded the motion, which was accepted unanimously

Summary Minutes - December 13-15, 2000

NTP Board of Scientific Counselors Report on Carcinogens Subcommittee

with 10 yes votes. Dr. Pelling moved that UVA be recommended for listing in the 10th *Report* as *reasonably anticipated to be a human carcinogen*. Dr. Smith seconded the motion, which was accepted unanimously with 10 yes votes. Dr. Smith moved that UVB be recommended for listing in the 10th RoC as *reasonably anticipated to be a human carcinogen*. Dr. Pelling seconded the motion, which was accepted by seven yes votes to three no votes (Froines, Kelsey, Moure-Eraso). Drs. Froines, Kelsey, and Moure-Eraso voted no because they thought the mechanistic information presented by Dr. Yamasaki supported a listing of *known to be a human carcinogen*. Dr. Pelling moved that UVC be recommended for listing in the 10th RoC as *reasonably anticipated to be a human carcinogen*. Dr. Smith seconded the motion, which was accepted by nine yes votes to one no vote (Dragan). Dr. Dragan thought there was insufficient human data to support listing of UVC in the RoC.

Trichloroethylene -- Dr. James Huff, NIEHS, presented the nomination and said that trichloroethylene (TCE) was first listed in the 9th RoC as *reasonably anticipated to be a human carcinogen* based on limited evidence in humans and sufficient evidence in animals. Subsequently, it was nominated for upgrading to *known to be a human carcinogen* in the 10th RoC by RG1 based on recently published human epidemiological studies supported by animal carcinogenicity and genotoxicity data as well as biological plausability. TCE is used primarily as a degreaser for metal parts with other uses based on its solvent properties. Annual production is 160,000 tons with exposure occupationally and via commercial products. With regard to human studies, the IARC (1995) pooled data from three occupational cohort studies showing excesses of liver and biliary cancer and non-Hodgkin's lymphoma, while two other studies had a two-fold increase of cervical cancer, and in the most recent study of cardboard manufacturing workers there was an excess of renal pelvis cancer, all leading to TCE's being classified as probably carcinogenic to humans (Group 2A). Dr. Huff then reported on four additional recent cohort studies in aircraft maintenance and manufacturing workers and uranium processing workers. He focused on a summary analysis by Wartenberg *et al.* that divided the cohort studies into three tiers based on the quality of the exposure data. Tier 1 were studies with urinary biomarkers, job exposure matrices, and job history. Conclusions were that relative risks were significantly elevated for multiple sites in cohort studies in Tier 1, the large size and long follow-up periods gave good exposure assessment of studies in Tier 1, and case-control studies available were supportive of cohort studies. Dr. Huff reported that in extensive animal studies, TCE by oral exposure causes liver tumors in mice and kidney and testes tumors in rats, while by inhalation exposure, liver and lung tumors and lymphomas are induced in mice, and kidney and testes tumors in rats. With regard to genotoxicity, TCE induces micronuclei and DNA single-strand breaks in mouse liver and kidney and rat liver. In mammalian cells *in vitro*, TCE induces cell transformations, sister chromatid exchanges, and gene mutations, while in peripheral lymphocytes of exposed workers, studies of genetic changes were inconclusive. Dr. Huff summarized various measures of biological plausability including concordance of cancer sites, similarity of metabolic pathways and major metabolites of TCE between humans and animals. He also reviewed Hill's Aspects of Causation with respect to TCE. Dr. Huff reported that RG1 voted unanimously with seven votes to recommend that the listing for TCE be upgraded to *known to be a human carcinogen* in the 10th RoC, while RG2 voted by three yes votes to four no votes against upgrading the listing in the 10th RoC. He said he believed that those opposing thought there was a lack of TCE-specific exposure assessment.

Public Comments: Dr. Trevor Green, Syngenta (formerly Zeneca) Central Toxicology Laboratory, United Kingdom, representing the Trichloroethylene Issues Group stated that exposure is a major issue in the proposed classification of TCE, yet there are not direct measurements of exposure in general epidemiology, toxicity, or genotoxicity studies. He said that exposure has been estimated in recall of physical symptoms 20 to 30 years after exposure ended. Further, Dr. Green commented that the animal data for the kidney are weak; there are no species, strain or tumor site concordances and the studies are inconsistent. Thus, he thought the existing data inadequate to classify TCE as a human carcinogen.

Summary Minutes - December 13-15, 2000

NTP Board of Scientific Counselors Report on Carcinogens Subcommittee

Dr. Paul Dugard, Halogenated Solvents Industry Alliance, Inc. (HSIA), presented two sets of comments, one from Professors Adami and Trichopoulos, Harvard University, regarding epidemiology, and the other from Dr. James Gnarra, Louisiana State University, and Dr. Cheryl Walker, University of Texas MD Anderson Cancer Center, concerning the von Hippel-Lindau (VHL) gene. Dr. Dugard stated that conclusions by the former on the cohort studies in general were that “evidence from epidemiologic studies in highly exposed humans does not provide any evidence to support an association between TCE and kidney cancer.” Drs. Gnarra and Walker had opined that multiple mutations in a single gene, in this case the VHL gene, are highly unlikely to confer selective advantage on a potential tumor cell clone. Furthermore, they believe that the finding of a “hot spot” mutation in apparent association with TCE exposure is potentially very significant, such that both findings have to be confirmed in independent studies with appropriate selection of subjects and the best possible assessments of exposure to TCE. Dr. Dugard concluded that the current evidence does not support classification of TCE as a known human carcinogen.

Dr. Jack Mandel, Exponent, Inc., representing the Chlorine Chemistry Council, stated that of the eight occupational cohort studies looking at kidney cancer, liver cancer, and non-Hodgkin’s lymphoma, seven did not find significantly increased risks of these cancers. Dr. Mandel said that the eighth, Henschler *et al.*, which was designed around a cancer cluster, and a case-control study by Vamvakas *et al.* reported significant risks for human cancer. However, he noted that both studies have so many methodological problems that no valid conclusions are possible.

Dr. Elizabeth Maull, U.S. Air Force, reported that their review focused on human studies published since the 9th RoC in which TCE is listed as *reasonably anticipated to be a human carcinogen*. She commented that their review failed to uncover evidence of causality based on Hill’s criteria for causality. Dr. Maull agreed with Dr. Mandel’s report that the seven good cohort studies provided risk estimates that centered around one, while also agreeing that the outdated epidemiologic methodology used by Henschler *et al.* and Vamvakas *et al.* does not meet current standards and is unacceptable.

Dr. Louis Bloemen, Dow Chemical Company, stated that the DBD completely and systematically ignores descriptions of historical worker exposure, and therefore, does not consider “all relevant information”. He noted that the document does extensively quote results from the meta-analysis publication by Wartenburg *et al.* (2000) but ignores careful comments from the authors which show clearly that the results of the analysis were not definitive.

Dr. Frederick said that Dr. Wartenberg was present and would like to respond to comments by the public and to any questions by the Subcommittee. Dr. Daniel Wartenberg, Robert Wood Johnson Medical School, agreed that there were problems with the Henschler *et al.* and Vamvakas *et al.* studies, but indicated that his review was intended to be comprehensive. He then commented on what have been called the Hill criteria for causality, but pointed out that in Hill’s original paper these are called aspects not criteria. Hill did not assert that they were all necessary to infer causality; in fact, he provided an example where only one was filled. The Hill aspects are not a checklist; instead they form a framework for thinking about causality.

Dr. Wartenberg also commented that the numbers presented by Dr. Mandel were for mortality in a restricted subset of the subjects in the Blair study, while the numbers in his review reflected both incidence and mortality in the entire group. In response to Dr. Bloeman’s comment about aggregating data, Dr. Wartenberg said that the intent of his review was to present an overall picture. This was done by presenting data from each of the articles included in the review and then using a weighted averaging approach to summarize the data, so both the data and summary are available in the review.

Summary Minutes - December 13-15, 2000

NTP Board of Scientific Counselors Report on Carcinogens Subcommittee

Dr. Wartenberg said that other speakers had reviewed the subject by counting how many papers were positive or negative, an approach called “vote-counting” that is not statistically sensitive or powerful and can be very misleading because the quality of the individual papers is not taken into account. The review on TCE was not intended to be a meta-analysis but to provide weighted averages that would be quantitative but nonetheless descriptive.

Dr. Smith commented that the question is how you interpret and use information, not what you label it. Regarding kidney cancer, he felt the strength of association was weak and the Bradford-Hill criteria of dose-response and specificity were not fulfilled. He asked for Dr. Wartenberg’s interpretation of the kidney cancer data. Dr. Wartenberg agreed that how averages were calculated was less important than how they were interpreted. In terms of the exposure concerns that many people had mentioned, his review stated that one limitation of all the studies was inadequate exposure assessment. He described the strength of the association as moderate because the average risks were between 1 and 2. In Tier 1, the average risks for kidney, liver, and non-Hodgkins lymphoma were 1.7, 1.9, and 1.5. It is difficult to observe a biologic gradient given that the exposure information in most studies was not good. His review found a preponderance of numbers greater than one despite all the limitations, suggesting that the results are not random.

Primary Reviewers: Dr. Zahm, a primary reviewer, did not agree with the proposed upgrading; rather, she thought TCE should remain listed as *reasonably anticipated to be a human carcinogen*. Of the eight new studies not considered in the evaluation of TCE for listing in the 9th RoC, she said five have only nonsignificant excesses. Another study reported a significant excess of malignant melanoma but had no data on sun exposure, complexion, number of sunburns, etc. The Henschler *et al.* and Vamvakas *et al.* studies are already acknowledged to have methodological problems and Dr. Zahm spoke of some additional weaknesses that had not been mentioned. She concluded by saying that there are ongoing, large-scale studies by IARC and the NCI that might provide a more definitive answer at a later date.

Dr. Bonney, also a primary reviewer, did not agree with the proposed upgrading, agreeing with Dr. Zahm that it should remain as listed as *reasonably anticipated to be a human carcinogen* in the 9th RoC.

Dr. Moure-Eraso, also a primary reviewer, agreed with the proposed upgrading. He said that all the data need to be looked at in concert, not just the epidemiologic but also the animal and mechanistic, in classifying the chemical. He argued that in observational mortality studies, all of their inherent problems (as described in the written review) are going to bias the studies toward the null, i.e., not finding correlations between exposure and cancer effect. These problems are: 1) misclassification of exposures; 2) dilution of rates, by including in exposed cohorts unexposed workers; and 3) healthy worker effect. Dr. Moure-Eraso proposed that in terms of public health, we should use the 95% confidence intervals as a way to make a decision. Further, he said that the speakers had discounted the German studies (Henschler *et al.* and Vamvakas *et al.*) even though they had been published in the peer reviewed literature. Dr. Froines said that we may be leaning too much toward trying to avoid false positives. In his experience, in occupational studies it is very difficult to do a good exposure assessment.

In other discussion, Dr. Kelsey suggested that the NTP consider trying to replicate the VHL data, arguing that if this could be done, he could support a future upgrading of the listing. He wondered if this were a situation where the mutation might be causal but not dose related, noting as example the *ras* oncogene and smoking-related lung cancer. Dr. Smith had doubts as to whether just TCE was the culprit since in many workplace settings other solvents are being used.

Dr. Zahm moved that the listing of trichloroethylene in the 10th RoC remain as *reasonably anticipated to be a human carcinogen*. Dr. Bonney seconded the motion, which was accepted with nine yes votes to one

Summary Minutes - December 13-15, 2000

NTP Board of Scientific Counselors Report on Carcinogens Subcommittee

no vote (Moure-Eraso). Dr. Moure-Eraso said that he had stated his reasons and would add to his review as a minority report.

Methyleugenol -- Dr. Ronald Melnick, NIEHS, presented the nomination and said that methyleugenol was nominated by RG1 for listing in the 10th RoC as *reasonably anticipated to be a human carcinogen* because two-year oral studies by the NTP (2000) showed *clear evidence of carcinogenic activity* in both sexes of rats and mice. Further, methyleugenol is structurally related to safrole, an agent listed in the RoC as *reasonably anticipated to be a human carcinogen* and by IARC as possibly carcinogenic to humans (Group 2B). Dr. Melnick said annual U.S. production was about 25,000 pounds. Methyleugenol is a natural constituent of many essential oils and is used as a natural or synthetic flavoring agent in many foods, as well as an attractant in insecticides and fragrance in perfumes and soaps. Dr. Melnick provided data on human blood/serum levels obtained from the National Health and Nutrition Examination Survey (NHANES III) and the National Occupational Exposure Survey (NOES). However, there are no studies of potential carcinogenicity of methyleugenol in humans. The NTP gavage studies included a stop exposure study in rats and resulted in increased incidences of liver tumors and glandular stomach neuroendocrine tumors in rats and mice, and renal tubule adenomas in male rats. Methyleugenol was also carcinogenic to the liver in the neonatal mouse model. Methyleugenol has been shown to produce positive effects in various genotoxicity assays including induction of unscheduled DNA synthesis in rat, mouse and human hepatocytes. Dr. Melnick presented information on metabolism to DNA reactive metabolites, and he noted that a mutated β -catenin gene, a gene identified as mutated in human hepatocellular cancers, was found to be increased in frequency in mouse liver tumors induced by methyleugenol. Dr. Melnick reported that RG1 (7 votes) and RG2 (8 votes) voted unanimously to recommend that methyleugenol be listed in the 10th RoC as *reasonably anticipated to be a human carcinogen*. Dr. Frederick asked whether there was evidence of *Helicobacter* infection in mice in the NTP study. Dr. Melnick replied that *Helicobacter* was indicated by PCR techniques and one of the liver cell lesions typically associated with *Helicobacter*, oval cell hyperplasia, was found in treated mice. However, this lesion was not distributed evenly across dosed and control groups in male mice, which would be expected if caused by an infection. The lesion was also found in female mice and rats, and staining for *Helicobacter* was negative.

Public Comment: Dr. Timothy Adams, representing the Flavor and Extract Manufacturers' Association (FEMA) and the FEMA Expert Panel, reported that after much research by the industry on methyleugenol and the related estragole, a workshop was convened by FEMA and the Research Institute for Fragrance Materials (RIFM) to review the state of the science, including the NTP study. He said the workshop concluded that: the NTP bioassay could not be used for assessing the safety of methyleugenol because: (1) the bioassay was performed at inappropriately high dose levels that caused hepatic dysfunction, significant gastric damage, and malnutrition, and recommended a new study at lower dose levels using a microencapsulated dosage form in the diet.

Primary Reviews: Dr. Medinsky, a primary reviewer, agreed with the proposed listing. She said the DNA-reactive mechanism of action implies that any dose of methyleugenol bears some risk of carcinogenicity. Dr. Medinsky suggested adding to the Summary Statement a comparison of blood levels in exposed rodents with levels measured in humans in the NHANES III study to provide some perspective as to the general order of magnitude between concentrations of methyleugenol that are carcinogenic in rodents with concentrations found in humans.

Dr. Dragan, also a primary reviewer, said the listing was on a borderline between possibly carcinogenic and the proposed listing. The data on unscheduled DNA synthesis in human hepatocytes was supportive of the latter, but she thought that further pharmacokinetic studies are needed to determine whether the metabolite 1-hydroxymethyleugenol is in human hepatocytes at human dose levels.

Summary Minutes - December 13-15, 2000

NTP Board of Scientific Counselors Report on Carcinogens Subcommittee

Dr. Bonney, also a primary reviewer, agreed with the proposed listing.

As a clarifying comment, Dr. Joseph Haseman, NIEHS, discussed body weight effects in the bioassay. He reported that there was little effect in male mice but about a 40% reduction in all dose groups of female mice, while in rats there were about 25% decrements below control by study's end. NTP speculated these decreases were likely due to toxicity of methyleugenol to the liver and glandular stomach. Dr. Medinsky pointed out that even at the lowest dose, there were carcinogenic effects. Dr. Haseman commented that this was one of the stronger carcinogens seen in the NTP Bioassay Program. Dr. Phillips noted that the chemical does appear to be an additive in foods popular with children and supported the principle of the proposed listing.

Dr. Medinsky moved that methyleugenol be recommended for listing in the 10th RoC as *reasonably anticipated to be a human carcinogen*. Dr. Bonney seconded the motion, which was accepted by nine yes votes to one no vote (Dragan). Dr. Dragan said that since this listing was for potential human carcinogenicity, there should be more evidence from human studies.

Metallic Nickel and Nickel Alloys -- Dr. Jameson prefaced the discussion by remarking that nickel compounds were reviewed by the Subcommittee in 1998 but listing in the RoC was deferred until the NTP could complete its review of metallic nickel and nickel alloys. Dr. Michael Waalkes, NCI at NIEHS, presented the nomination and said that nickel and certain nickel compounds were listed in the 9th RoC as *reasonably anticipated to be human carcinogens*, and this listing includes metallic nickel as well. This review completes the evaluation of nickel and nickel compounds for listing in the 10th RoC. IARC had evaluated metallic nickel as possibly carcinogenic to humans in 1990, and more recently (1999) nickel alloys, in particular the alloy containing 66-67% nickel, 13-16% chromium, and 7% iron were also considered as possibly carcinogenic to humans. With regard to human exposure from both occupational and environmental sources, about 725,000 workers are potentially exposed to the various forms of nickel. Sources of occupational exposure are varied and include the processes associated with mining and refining as well as production uses. Sources of environmental exposure include atmospheric emissions, tobacco smoke, and contaminated food and water. Metallic nickel carcinogenesis in animals is evidenced by multiple studies inducing lung carcinomas after intratracheal instillation, local sarcomas or mesotheliomas after subcutaneous, intramuscular or intraperitoneal injections, with several studies showing a dose-response relationship. Similar findings were reported for several different nickel alloys with alloys of higher nickel content more likely to produce tumors. Dr. Waalkes reported that there are no adequate epidemiological studies of exposed workers evaluating carcinogenicity of metallic nickel or nickel alloys. The literature indicates that there is little excess cancer risk associated with metallic implants or prostheses containing nickel. With regard to possible carcinogenic mechanisms, nickel in one form or another, can cause chromosomal aberrations, malignant cellular transformation, mutation, chromosomal damage, chromatin condensation, DNA damage, and disrupted DNA repair with the ionic form likely the active genotoxic species. Dr. Waalkes reported that RG1 voted with six yes to two no votes to recommend listing metallic nickel and certain nickel alloys in the 10th RoC as *reasonably anticipated to be human carcinogens*. RG2 voted with seven yes to one no vote to recommend listing metallic nickel as *reasonably anticipated to be a human carcinogen*, while voting with six yes to two no votes to recommend not listing certain nickel alloys. The majority in RG2 felt there were inadequate data to list nickel alloys in the RoC.

Public Comments: Mr. Michael Gipko, J&L Specialty Steel Inc., said that his company is a primary consumer of nickel and misclassifying nickel alloys as carcinogens would have a devastating impact on the stainless steel industry. He emphasized that NTP decisions lead to regulatory actions in the U.S. and the rest of the world leading to widespread social and economic impacts. Mr. Gipko stated that because of these impacts, the Subcommittee has a legal duty to ensure that its decisions are based on sound science and the product of reasoned decision-making before stigmatizing a substance as a carcinogen.

Summary Minutes - December 13-15, 2000
NTP Board of Scientific Counselors Report on Carcinogens Subcommittee

Mr. Joseph Green, Collier Shannon Scott, PLLC, representing the Specialty Steel Industry of North America stated that long-term human experience provides ample evidence that nickel and nickel alloys, like stainless steel, do not pose a cancer risk to humans through routes of exposure relevant to humans. Further, he said it is not appropriate to group all nickel alloys together as the unique properties of each alloy affect the release rate and bioavailability of individual metal ions.

Dr. Adriana Oller, Nickel Producers Environmental Research Association (NIPERA), commented that the release rate or even carcinogenic potential for an alloy is going to be related to the chemical composition of other elements and physical attributes, not just nickel content. She said that potential carcinogenicity also is influenced by the form in which exposure occurs. Dr. Oller concluded by returning to soluble nickel, which had been discussed briefly at the previous review of nickel by the Subcommittee and recommended to be listed as *known to be a human carcinogen*. She reported that a recent assessment by Toxicology Excellence for Risk Assessment determined that carcinogenicity of soluble nickel by inhalation and oral routes could not be determined, and requested a reconsideration.

Mr. Neil King, INCO United States, Inc., disputed NTP's statement that there are very little relevant epidemiological data for metallic nickel. He cited cohort studies from before 1990, and four cohort studies since 1990, one involving 31,000 nickel alloy workers in which there was no indication of increased respiratory cancer risk. These and other cohorts were reviewed by the International Committee on Nickel Carcinogenesis (ICNC), which also concluded there was no evidence that metallic nickel was associated with increased lung and nasal cancer risks. Further, Mr. King stated that current occupational exposures are going to be lower than those in the earlier epidemiology studies. In response to an inquiry from Dr. Frederick, he said the epidemiology studies were in the published literature, but failed to provide the reference.

Dr. Michael Dourson, Toxicology Excellence for Risk Assessment (TERA), said TERA is a nonprofit group whose mission is to protect public health, and was asked by EPA, Metal Finishing Association of Southern California, and Health Canada to develop a soluble nickel salt risk assessment document. He described the peer review process which was conducted by an expert panel in a public setting. The panel's conclusion was that carcinogenicity of soluble nickel by oral or inhalation routes could not be determined. Dr. Frederick noted that the presentation was not relevant to the agenda topic, metallic nickel. Dr. Smith disagreed, and Dr. Frederick acknowledged that soluble nickel might be looked at as the biologically active form of the metal.

Ms. Donna Sivulka, environmental consultant, representing the International Nickel Corporation (INCO United States) amplified the post-1990 epidemiologic studies of metallic nickel referred to by Mr. King. She noted that the 31,000 worker study, published in 1998, and other more recent studies were not cited in the DBD. She said it is difficult to separate out workers exposed to metallic nickel and those exposed as well to other nickel compounds. Ms. Sivulka emphasized that besides the metallic nickel-exposed workers there are not many other people who will be exposed to metallic nickel, and for these workers excess respiratory cancer rates are not being seen.

Dr. William Allaben, FDA/NCTR, submitted a statement from the FDA Center for Devices and Radiological Health that the Center agrees with the listing in the 10th RoC of metallic nickel and certain nickel alloys as *reasonably anticipated to be human carcinogens* and with the statement in the DBD that studies generally suggest that there is little excess risk of carcinogenicity associated with orthopedic implants. Dr. Freja Kamel offered comments on why the studies on prostheses and implants were basically uninterpretable in ruling out the possibility of cancer causation. First, there was a lower total cancer risk for the entire cohort, which may be due to the "healthy patient effect"; second, these studies had very few cases for the relevant sites, and a relatively short follow-up time, since it was primarily an

Summary Minutes - December 13-15, 2000
NTP Board of Scientific Counselors Report on Carcinogens Subcommittee

older population; and third, the studies generally did not differentiate metal/metal implants vs. metal/polyethylene implants. The former type releases more particles of nickel into the circulation.

Primary Reviewers: Dr. Phillips, a primary reviewer, agreed that the animal data supported the proposed listing for metallic nickel and that intratracheal instillation is a reasonable model for human inhalation studies. He had an uncertainty over the use of the term “certain alloys”, and whether or not the behavior of nickel can be predicted from its chemical content in an alloy. Dr. Phillips commented that although skin sensitization studies indicate some release, he did think that the use of low nickel containing alloys in prosthetic devices as unlikely to be of significant risk.

Dr. Kelsey, also a primary reviewer, agreed with the proposed listing based on the animal and *in vitro* data which are very clear in presenting evidence of significant carcinogenic potential via multiple routes of administration in multiple species. He said that what epidemiologic evidence exists is consistent with little excess cancer risk. Dr. Kelsey suggested the possibility that metallic nickel alloys act as carcinogens via an epigenetic route be mentioned.

Dr. Froines, also a primary reviewer, agreed with the proposed listing for metallic nickel, but remained uncertain as to certain nickel alloys. He noted the paucity of data and the complexity of the alloys. The 1990 IARC review concluded there was limited evidence in experimental animals for the carcinogenicity of nickel alloys and the 1999 IARC does not provide sufficient additional evidence to draw a different conclusion.

In clarifying discussion, Dr. Jameson acknowledged that nickel and certain nickel compounds were listed in the 1st *Report on Carcinogens* in 1980, and were reviewed again in 1998 on the basis of information that had become available since 1980. Metallic nickel and certain nickel alloys were not included in the 1998 review and that is why they are being reviewed at this meeting. In response to queries about the definition of “Certain Nickel Alloys”, Dr. John Bucher, NIEHS, said the third paragraph of the Summary Statement in the DBD provides a concise sense of what is meant while indicating the complexity of the issue. Dr. Phillips opined that he didn’t think the Subcommittee could take a vote and then let the NTP work out what it was they voted on. Dr. Bonney proposed tabling the nomination of certain nickel alloys until the next meeting. Dr. Smith did not give much credence to the various injection studies and also commented that nickel and other metals found to be carcinogenic were in the salt form, as for example, nickel oxide and sulfide. Dr. Waalkes observed that various injection routes can give some indication of carcinogenic potential even though some of these would not be a likely route of human exposure. Dr. Zahm commented that with the nickel alloys there are cases where there are actually negative human data and not just nonexistent data, which could speak against the proposed listing. Dr. Kelsey cautioned that for some alloys there would not be negative data. Dr. Frederick announced that there would be separate motions for metallic nickel and certain nickel alloys.

Dr. Kelsey moved to recommend metallic nickel be listed in the 10th RoC as *reasonably anticipated to be a human carcinogen*. Dr. Froines seconded the motion, which was accepted with seven yes to three no votes (Bonney, Dragan, Smith). Dr. Dragan said that nickel salts under certain conditions are carcinogenic whereas she didn’t see evidence to support metallic nickel. Dr. Smith said there were insufficient animal data and no inhalation studies. He disagreed that soluble nickel causes cancer and noted that it is an element found in all cells.

Dr. Kelsey then moved to recommend that certain nickel alloys be listed in the 10th RoC as *reasonably anticipated to be human carcinogens*. Dr. Moure-Eraso seconded the motion. At Dr. Medinsky’s suggestion, Dr. Kelsey amended the motion to define “certain” to include bioavailability and bioactivity. Dr. Moure-Eraso agreed to the change. Dr. Phillips commented that unless one is more specific, e.g., alloys with 50% or more nickel, it shouldn’t go forward. Dr. Moure-Eraso was concerned that would

Summary Minutes - December 13-15, 2000

NTP Board of Scientific Counselors Report on Carcinogens Subcommittee

move us toward risk assessment. Dr. Carpenter noted that it was not just the nickel content but also inclusion of other metals in the alloy that affects the release of nickel ions. The amended motion remained: “to list certain nickel alloys as defined by bioavailability and bioactivity as *reasonably anticipated to be a human carcinogen*”. The motion was defeated by seven no to three yes votes (Carpenter, Kelsey, Moure-Eraso). Dr. Froines moved that certain nickel alloys not be listed in the 10th RoC. Dr. Medinsky seconded the motion, which was accepted by nine yes votes to one no vote (Kelsey). Dr. Kelsey said he thought certain nickel alloys should be listed as *reasonably anticipated to be a human carcinogen*.

Chloramphenicol -- Dr. Haseman presented the nomination and said that chloramphenicol was nominated by RG1 for listing in the 10th RoC as *reasonably anticipated to be a human carcinogen* based primarily on the IARC listing as probably carcinogenic to humans (Group 2A). He said it was the first antibiotic to undergo large scale production in the late 1940s but fell into disfavor after evidence mounted that it caused potentially fatal aplastic anemia, and is now used only to combat serious infections where other antibiotics are ineffective or contraindicated. It is used in veterinary medicine but prohibited in food producing animals. With regard to human cancer, Dr. Haseman said the first evidence was many case reports documenting the occurrence of aplastic anemia and leukemia following treatment with chloramphenicol, and three case reports documenting occurrence of leukemia in the absence of aplastic anemia. He reported on two more definitive case-control studies, one a NCI population-based study in Shanghai that found elevated risks of childhood leukemia associated with chloramphenicol therapy, and the second finding elevated risks of soft tissue sarcoma in Kansas men associated with exposure. The studies taken collectively support a conclusion of increased cancer risk associated with exposure to chloramphenicol, and children may be a susceptible subgroup. Dr. Haseman said the animal data were very limited, with there being one abstract that reported elevated rates of lymphoma and liver tumors in two strains of mice but the study was incompletely reported. With regard to genotoxicity, chloramphenicol is negative in bacterial systems, produces mixed results in mammalian systems, and is consistently positive in producing DNA single-strand breaks and increased frequencies of sister chromatid exchanges and chromosome aberrations. Dr. Haseman reported that RG1 voted unanimously with seven votes, and RG2 cast seven yes votes with one abstention to recommend listing chloramphenicol in the 10th RoC as *reasonably anticipated to be a human carcinogen* based on evidence from human studies.

Public Comments: None.

Primary Reviews: Dr. Pelling, a primary reviewer, agreed with the proposed listing based on limited evidence of carcinogenicity from human studies. Many of the studies rely on patient or family member recall to confirm exposure to chloramphenicol, and the Kansas study had a very small number of exposed individuals. Dr. Pelling asked that information be added to the DBD about the significantly elevated risk of developing aplastic anemia in chloramphenicol treated individuals.

Dr. Smith, also a primary reviewer, agreed with the proposed listing. He thought the Chinese study that showed a close to doubling in occurrence of childhood leukemia after such short term exposure to chloramphenicol astonishing, and was puzzled that there have not been other studies. However, Dr. Smith thought the aplastic anemia evidence to be compelling and supportive.

Dr. Carpenter, also a primary reviewer, agreed with the proposed listing. Given that chloramphenicol could be a useful model to study the possible link between several types of anemia and leukemia, he was surprised that there are not a lot more animal data available. Dr. Carpenter observed that there is a very large cohort available for additional epidemiological work given the worldwide use of chloramphenicol.

In further discussion, Dr. Zahm, who was a principal investigator for the study on soft tissue sarcomas in Kansas men, noted that their paper indicated there was considerable potential for misreporting on this

Summary Minutes - December 13-15, 2000

NTP Board of Scientific Counselors Report on Carcinogens Subcommittee

drug and thought this should have been pointed out in the DBD. However, she did agree with the proposed listing. Dr. Phillips asked, given the paucity of animal data, whether the NTP had considered doing a bioassay. Dr. Haseman responded in the affirmative, but it was not selected due to limited human use. Dr. Frederick stated that the astounding potency profile strained his belief in its credibility. Dr. Carpenter suggested that the Subcommittee should make a recommendation that further research is warranted. Dr. Smith said that advantage should be taken of various tumor registries around the world. Dr. Dragan commented that there should have been more information on veterinary epidemiology. Dr. John Singh, EPA, reported that chloramphenicol is a very useful drug in veterinary practice. Dr. Pelling asked whether dogs get aplastic anemia. Dr. Singh said they do, but more study is warranted.

Dr. Pelling moved to recommend that chloramphenicol be listed in the 10th RoC as *reasonably anticipated to be a human carcinogen*. Dr. Carpenter seconded the motion, which was accepted unanimously with 10 votes.

Talc (Asbestiform and Non-asbestiform) -- Dr. Portier announced that the NTP presentation on talc with asbestiform fibers followed by public comments and other discussion would lead off, and then the NTP presentation on talc without asbestiform fibers would be made followed by public comments and discussion. Primary reviews would be next. Dr. Frederick said that separate votes on the two types of talc would take place at the end.

Talc Containing Asbestiform Fibers: Dr. James Huff presented talc containing asbestiform fibers, which was nominated by RG1 for listing in the 10th RoC as *known to be a human carcinogen* based on the IARC listing of asbestiform talc as Category 1 (Known Human Carcinogen). He said the main supporting evidence was human epidemiology studies and case reports showing evidence of lung cancers and a few mesotheliomas in miners and millers with some limited evidence in experimental animal data as well as biological plausibility. Dr. Huff reported that talc is naturally occurring worldwide with each talc deposit unique in chemistry and morphology but containing other minerals. Simply defined, talc is a hydrous, inorganic mineral consisting largely of magnesium silicates. Talc containing asbestiform fibers is defined as talc typically made up of talc mineral, non-asbestiform tremolite or anthophyllite, Serpentine, Quartz, and trace amounts of "other" asbestiform fibers, but should not contain asbestos. He said that annual production is 1.25 million tons coming mostly from four states. Dr. Huff said that in the U.S., about 94% is used commercially in rubber, paints, plastics, paper, ceramics, and construction materials, while about 6% is used in consumer applications primarily pharmaceuticals, foods and cosmetics. Occupational exposures occur during mining, milling, and processing of talc, and in a wide variety of secondary industries as mentioned. He noted that through improvements in industrial hygiene and technology, such as wet drilling, exposure levels have been greatly reduced such that the current OSHA standard for "asbestiform talc" is only 0.1 fiber/cm³. He said that the primary human carcinogenicity studies derive from the 1987 IARC evaluation, which was based on case reports associating exposure with mesothelioma and two cohorts of talc miners and millers of talc containing asbestiform tremolite, or tremolite or tremolite anthophyllite and serpentine minerals in New York state that reported excess lung cancers. IARC classified talc containing asbestiform fibers as "carcinogenic to humans" (Group 1). Since 1987, there have been 10 studies of workers exposed to talc and most were consistent with IARC findings of modest increased risks of lung cancer with increased risk strongest for talc containing asbestiform fibers. Potential confounder factors include exposures to other lung cancer agents such as radon and silica. With regard to experimental carcinogenesis, talc of different grades was tested for carcinogenicity in rodents by various routes: injections, inhalation, oral, and instillation with most studies considered inadequate for various reasons. More recently, an NTP inhalation bioassay done with high purity talc resulted in lung cancers in female rats, adrenal gland cancers in male and female rats, and no talc-associated tumors in mice. There was no evidence for genotoxicity of cosmetic grade talc. Dr. Huff reported that RG1 voted unanimously with seven votes to recommend listing talc containing asbestiform fibers in the 10th RoC as *known to be a human carcinogen*, while RG2 voted with six no votes to two yes

Summary Minutes - December 13-15, 2000

NTP Board of Scientific Counselors Report on Carcinogens Subcommittee

votes for the same motion. RG2 then voted by six yes votes to two no votes to recommend listing talc containing asbestiform fibers in the 10th RoC as *reasonably anticipated to be a human carcinogen*.

Dr. Frederick said that volumes of public comments were received on this nomination and he wished to comment on some of them. One stated that the DBD was mineralogically superficial and uninformed. It was suggested that the definition for physical characteristics of asbestiform mineral fibers proposed by the American Society for Testing Materials (ASTM) should be used, and he cited the physical characteristics for asbestiform mineral fibers. Dr. Froines and Dr. Kelsey thought the Subcommittee should stick with the NTP definition. Dr. Carpenter and Dr. Medinsky thought the NTP definition was confusing.

Dr. Daniel Crane, OSHA, reported that his agency's definitions are parallel to and built in concert with the ASTM. He said that asbestiform is not a material but a mineral habit, i.e., the way something crystallized in nature. Dr. Crane commented that pure talc is a relatively well-defined magnesium silicate, as defined by Dr. Huff, while commercial talc may contain a lot of other minerals. Dr. Zahm noted that the six minerals classified as asbestos can exist without being asbestiform, and wondered if there are minerals that can be asbestiform without being asbestos. Dr. Crane replied affirmatively that this was usually the case, and generally, the asbestiform part of talc is composed of those fibers that are asbestiform but not one of the six minerals regulated directly by the OSHA asbestos standard. After more discussion about the definition, Dr. Crane suggested changing the title of the document to read "talc containing non-asbestos asbestiform fibers." There seem to be wildly divergent views across laboratories as to what is in a product, he said. Dr. Phillips asked what happens to the fibers when talc is milled. Dr. Crane replied that they get longer and thinner, which is characteristic of asbestiform fibers.

Public Comments: Dr. Robert Nolan, Environmental Sciences Laboratory, Brooklyn College, stated that the nomenclature of asbestiform talc is not specific enough to define a class of carcinogens, and the proper nomenclature should be fibrous talc and transitionals. He said that microscopic analyses indicate the fibrous particulates in talc are not surrogates for asbestos, and this fact is further substantiated by the results of several animal studies which indicate significant differences in that fibrous talc and transitionals lack the carcinogenic potency of asbestos fibers. As such, he claimed that fibrous talc and transitionals do not meet the criteria for inclusion in the NTP *Report on Carcinogens* and should be removed from further consideration.

Dr. Graham Gibbs, Safety Health Environment International Consultants Corp., presented an evaluation of the epidemiological evidence concerning talc and respiratory cancer with specific attention to talc as produced by the Gouverneur Talc Company (GTC) at its mines in New York State. He said that the overall excess in lung cancer in cohorts of GTC workers is not explained, although it is clear that a statistically significant excess of lung cancer is present in underground miners but not in millers. Dr. Gibbs concluded that, collectively, the currently available epidemiological studies of GTC workers do not support a causal relationship between GTC talc and respiratory cancer. Dr. Frederick noted that one of the key studies cited in support by Dr. Gibbs has never been published in the peer reviewed public literature.

Mr. John Kelse, R.T. Vanderbilt Company, Inc., said he would discuss the talc produced by GTC, a wholly owned subsidiary of his company, and which he titled "Vanderbilt talc." He claimed that the nomination by NTP of "talc containing asbestiform fibers" was based almost entirely on Vanderbilt talc, and he reviewed its actual composition. Mr. Kelse concluded that no animal, cell or human study seen by them reasonably demonstrated a carcinogenic risk for Vanderbilt talc similar to the asbestos risk.

Dr. John Gamble, Caldera Associates, on behalf of R.T. Vanderbilt Company, Inc., said that in sum, the weight of the evidence from the various studies does not satisfy the criteria for a causal relationship between Vanderbilt talc exposure and risk of lung cancer. The associations are weak and elevated risks

Summary Minutes - December 13-15, 2000
NTP Board of Scientific Counselors Report on Carcinogens Subcommittee

could be due to chance or confounding by smoking. The temporality criterion is more consistent for a smoking etiology than for a talc etiology.

Dr Ann Wylie, University of Maryland, said she wanted to bring a mineralogist's perspective to what is being considered. Mineralogists refer to the material occurring in the New York state talc deposit as fibrous talc all by itself or intergrown with amphibole, which may be anthophyllite or tremolite, and intergrown with other undefined minerals. She said that asbestiform does not mean having the properties of asbestos but rather is a habit, and different asbestiform minerals have different properties.

Talc Not Containing Asbestiform Fibers: Dr. Freya Kamel, NIEHS, presented the nomination and said that talc not containing asbestiform fibers was nominated by RG1 for listing in the 10th RoC as *reasonably anticipated to be a human carcinogen* based on epidemiological studies showing some evidence of an association between talc use and ovarian cancer in women, and on the NTP Technical Report showing evidence of carcinogenicity in rats. Dr. Kamel reported that cosmetic talc, which is the exposure considered in many of the studies, is defined as powdered magnesium silicate with 98% of the particles less than 200 mesh, containing no amphiboles. Talc is an included ingredient in many cosmetic products, among them being loose powders, creams, lotions, makeup, antiperspirants, lipstick, and eye shadow. Other consumer and industrial applications were mentioned previously by Dr. Huff. Dr. Kamel said that most of the evidence for the nomination comes from human cancer studies, basically of two types. There are 16 case control studies and one cohort study looking at ovarian cancer and genital exposure to talc. She continued that there were occupational studies that looked at talc thought not to contain asbestiform fibers, including one case control study of ovarian cancer and two cohort studies of lung cancer. Dr. Kamel provided more detailed information on the two types of studies. There was consistent evidence for association of ovarian cancer with genital exposure to cosmetic talc, while bias and confounding were not likely but could not be excluded. In general, studies of occupational exposure did not provide support for an association of talc exposure with increased cancer risk. Dr. Huff had previously described experimental carcinogenesis studies, primarily the NTP inhalation study in rodents. Dr. Kamel said as far as mechanisms underlying ovarian cancer, inflammation may be a general mechanism. She reported that RG1 voted with six yes votes to one no vote, and RG2 voted with seven yes votes to one no vote to recommend listing talc, not containing asbestiform fibers, in the 10th RoC as *reasonably anticipated to be a human carcinogen*.

There ensued a clarifying discussion on the nature or composition of the talc used in the ovarian cancer studies. Dr. Frederick wondered whether all the studies were done with non-fibrous talc or whether some used fibrous. Dr. Kamel responded that before 1976, some samples of talcum powder were found to contain up to 30% fibrous materials, while after 1976 there had been voluntary guidelines suggesting that cosmetic talc should not contain such fibers. Further, she said that most studies including the cohort study weren't able to analyze the talc, as they based their exposure estimates on questionnaire data. Dr. Zahm noted that ovarian cancer has a long latent period so you would likely have exposures before and after the voluntary guidelines. Dr. Smith inquired as to whether a meta-analysis had been done, and Dr. Kamel replied that none had been published but that one of the public comments included a meta-analysis that found a statistically significant increase in risk of 1.3. Dr. Froines, relating from his personal experience in Vermont talc mines, pointed out that in the ore, you don't find asbestos, but in the material surrounding the talc deposits there are considerable amounts of asbestos to which miners could be exposed.

Public Comments: Dr. Harris Pastides, University of South Carolina, representing the Cosmetic, Toiletry, and Fragrance Association (CTFA) said he and his associates were asked to evaluate credibility of the epidemiological evidence in the published literature related to the potential that talc use may cause ovarian cancer. He reported that a weighted average of the results of the 17 epidemiologic studies measuring the relation gives an overall risk of 1.31, with a 95% confidence interval of 1.21-1.41. Bias

Summary Minutes - December 13-15, 2000

NTP Board of Scientific Counselors Report on Carcinogens Subcommittee

and causation are competing explanations for the weak positive association observed. Further, he said the lack of a plausible biologic mechanism weighs against a causal interpretation.

Dr. Judith Jones, The Degge Group, Ltd., representing the U.K. Cosmetic, Toiletry, and Perfumery Association reviewed the epidemiologic evidence in support of an association between ovarian cancer and use of talc products. She stated that although some of the studies suggest an increased risk of ovarian cancer after exposure to talc, the risk estimates are almost all borderline or not significant. Further, Dr. Jones said they are based on relatively imprecise measures of exposure that do not show a dose-response relationship, and do not typically take all risk factors into consideration. She concluded that there is not sufficient evidence based on the available data that talc in fact poses a risk for ovarian cancer.

Mr. William Kelly, Center for Regulatory Effectiveness, said that he was commenting solely on the proposal to list talc, not containing asbestiform fibers as *reasonably anticipated to be a human carcinogen.*, which requires at least limited evidence in humans and/or sufficient evidence in animals. He observed that the Background Document admits that none of the human ovarian cancer studies are usable. Mr. Kelly said the 1993 NTP rodent bioassay findings were addressed by a workshop cosponsored by the FDA and the International Society of Regulatory Toxicology and Pharmacology and the consensus was that the results were likely experimental artifact and non-specific generic response of dust overload of the lungs and not direct activity of talc.

Dr. Günter Oberdörster, University of Rochester, representing Colipa Europe, presented data suggesting that pulmonary response to inhaled talc in rats is like that of other poorly soluble particles (PSPs), and that the mechanism of lung tumor induction in rats is due to high dose overload-induced inflammation leading eventually to secondary genotoxicity; these secondary genotoxic mechanisms are not operative in other species including humans. He said that increased lung tumors in female rats should not be considered sufficient evidence that talc is *reasonably anticipated to be a human carcinogen.* Dr. Zahm asked why male rats did not respond the same. Dr. Oberdörster responded that male rats are bigger and female rats generally respond earlier to PSPs. Dr. Phillips asked for an explanation of the secondary genotoxicity. Dr. Oberdörster said the release of PMN (polymorphonuclear) neutrophils have been shown to induce DNA damage.

Mr. John Addison, John Addison Consultancy, representing the Scientific Association of the European Talc Industry, hoped that the NTP had addressed serious deficiencies in the DBD pointed out by himself and Dr. Arthur Langer, Brooklyn College, in a written submission. Mr. Addison said that “asbestiform talc” exists but as a very rare mineralogical curiosity. Further, he stated that with the combination of selected mining, minerals processing, and quality control in the talc industry there is no widespread contamination of talc products by asbestos. Thus, he believed that there is no justification for the nomination of talc for listing. Drs. Carpenter and Pelling said his statement about the rarity of asbestiform talc was at variance with information given earlier. Mr. Addison said he believed the information they referred to was historical and not on the present day situation. Dr. Crane noted that there is obviously a difference between what the companies are marketing and what miners are exposed to.

Dr. Allan Gibbs, Llandough Hospital, U.K., representing EuroTalc, presented information on a peer reviewed study of talc workers in Luzenac encompassing over 30,000 person-years of exposure to talc that is primarily amphibole free and showing no statistically significant excess of lung cancer. Dr. Gibbs also discussed talc pleurodesis, a practice of putting talc into the pleural cavity of humans for therapeutic purposes, for which 65 years of experience have shown negative risk for lung cancer and mesothelioma.

Dr. Roger McClellan, Inhalation Toxicology and Human Health Risk Analysis, representing Mineral Technologies, Inc., said the DBD is confusing with regard to nomenclature, particularly in distinguishing between asbestiform and non-asbestiform minerals. He said the epidemiological data does not meet the

Summary Minutes - December 13-15, 2000

NTP Board of Scientific Counselors Report on Carcinogens Subcommittee

NTP criteria for limited evidence with an indication of a causal interpretation that is credible. With regard to animal evidence, the NTP bioassay, Dr. McClellan opined that both high and low doses may have exceeded the Maximum Tolerated Dose, and the finding of lung tumors in female rats relates to an overload phenomena and of pheochromocytomas relates to a stress phenomena. Dr. Medinsky asked whether the effects in rats were analogous to the alpha-2- μ -globulin relationship to renal tumors in male rats. Dr. McClellan agreed that was another good example of a rat specific effect. Dr. Yamasaki said we really don't know the mechanism for carcinogenesis and thought the tumors in rats represent a quantitative difference in exposure from humans. Dr. McClellan replied that the experience with coal miners exposed to very substantial burdens of coal dust yet not an increased risk of lung cancer argues otherwise. Dr. Phillips asked whether sizes of particles of coal dust were similar to those of talc used in the animal studies. Dr. McClellan said some of the coal particles would be in the 3 micron range.

Primary Reviews: Dr. Froines, a primary reviewer, said that prior to the day's discussion he had been prepared to support a listing of *known to be a human carcinogen* for talc containing asbestiform fibers but now reserved judgment. He said that we may be voting on a historical rather than a current issue. With regard to non-asbestiform talc and ovarian cancer, he said that is not so clear either, since it is possible that some of the cosmetic talcs were contaminated with asbestos or other products, although he was reassured that the talc used in the NTP bioassay was fairly pure. Dr. Froines stated that what concerned him was that, since the OSHA and MSHA legal standard is 5 mg/m³, humans could be exposed within an order of magnitude of the levels used in the bioassay. Therefore, he recommended either listing talc as *reasonably anticipated to be a human carcinogen* with a subparagraph that it is likely to be a carcinogen at doses exceeding 1 mg/m³ based on overload., or creating a separate category describing talc as an animal carcinogen at high doses.

Dr. Carpenter, also a primary reviewer, said he was particularly concerned about the potential for historical asbestos contamination of the cosmetic talc. With regard to talc containing asbestiform fibers, he would support *reasonably anticipated to be a human carcinogen* based on epidemiological studies of exposed workers as the limited evidence indicating a causal relationship is credible. However, animal data are lacking. With regard to talc not containing asbestiform fibers, Dr. Carpenter could support *reasonably anticipated to be a human carcinogen* based on the ovarian cancer data although he had questions as to why there was not cancer at other sites and as to a suggestion of a reasonable mechanism of action.

Dr. Medinsky, also a primary reviewer, said that listing talc in the *Report* is not a straightforward issue, and this was before she heard all the comments made in this meeting. With regard to epidemiology studies associating exposure to talc with lung cancer, she noted that each are confounded by simultaneous exposure to other known human lung carcinogens, while for studies associating exposure to talc and ovarian cancer, the lack of a consistent strength of association increases uncertainty regarding a causal relationship. With regard to mechanistic studies, Dr. Medinsky found data suggesting that talc is able to migrate through the female genital tract to the ovaries and peritoneal cavity to be unconvincing. Finally, she thought the laboratory animal data when interpreted for human relevance supported limited evidence for carcinogenicity of talc. Thus, Dr. Medinsky said she would support not listing talc.

In further discussion, Dr. Froines reiterated his position that if he could not add a caveat pertaining to a high dose phenomenon in the miners and talc workers, he would vote for *reasonably anticipated to be a human carcinogen* without it. Dr. Zahm said she would agree with Dr. Medinsky that there is not sufficient evidence in animals to support listing of non-asbestiform talc, while for the asbestiform talc, the best data were the NIOSH study in New York, and after the earlier discussion, it was unclear whether the talc miners were or were not exposed to asbestos. Dr. Mark Toraason, NIOSH, reported that he had talked to a co-author on the NIOSH study in New York who said the workers were initially exposed to asbestos mineral, and then during the mining/milling process fibers were formed with an aspect ratio of

Summary Minutes - December 13-15, 2000

NTP Board of Scientific Counselors Report on Carcinogens Subcommittee

one to three and a length of $> 5\mu$. Dr. Pelling referred to a key reference by Lamm *et al.* cited in the DBD in support of the proposed listing for talc containing asbestiform fibers and recent correspondence from Dr. Lamm concerning misinterpretation of his 1988 paper. Dr. Dana Loomis, University of North Carolina, who was a contributor to the epidemiology section of the DBD, said he believed Dr. Lamm's difference of opinion related to the reliance of the DBD on the numerical data rather than his written interpretation. Dr. Steven Lamm commented that his disagreement had to do with the authors of the DBD not paying attention to his sub-analysis. Further, he said that a second paper, which would have been helpful, was not cited. Dr. Lamm said the first paper showed that there was an elevated lung cancer risk in the study cohort for both long-term and short-term (less than one year on the job) workers, but the risk was statistically significant only in the short-term workers. He said the second paper established that the short-term workers brought the risk with them. Dr. Loomis reiterated that the DBD was based on the data in Dr. Lamm's papers and not Dr. Lamm's interpretation of the data.

There was some disagreement among members of the Subcommittee as to whether there were qualitative or quantitative differences in carcinogenic responses to non-asbestiform talc between rats and humans. Dr. Portier said that because of the potential contamination of the talc used in the ovarian cancer studies, alternative explanations such as chance, bias or confounding factors could not adequately be excluded, and its still limited evidence. Dr. Zahm said that you couldn't rule out confounding; however, the definition of exposure is uncertain as it relates to whether or not the talc women were exposed to contained asbestos. Dr. Smith commented that it was not only whether or not there was contamination, and by what and how much, but also the temporal aspects leading in his mind to consideration of deferral. Dr. Moure-Eraso wondered if talc from some of the studies could be obtained and analyzed for contaminants. Dr. Zahm said the ovarian cancer studies were interview studies using questionnaires and talc samples would not be available. Dr. Crane reported that in the studies showing whether or not there was talc in the ovaries, what was reported was talc, not asbestos or asbestiform. Dr. Phillips opined that the definitions made earlier made it clear what is meant by talc containing asbestiform fibers and talc not containing asbestiform fibers, and that asbestos itself is not in the mix. Dr. Dragan commented that if one looks at neoplasia only, there is a high dose phenomena in female rats but if non-neoplastic lesions, there are extreme biologic responses at both doses in both sexes, analogous to humans.

Motions: Dr. Smith moved that the nomination of talc, containing asbestiform fibers, not containing asbestos for listing in the 10th *Report* be deferred. The motion failed for lack of a second. Dr. Froines moved to recommend that talc, containing asbestiform fibers, not containing asbestos be listed in the 10th RoC as *reasonably anticipated to be a human carcinogen*. Dr. Carpenter seconded the motion. Dr. Medinsky inquired as to what studies formed the basis of the motion. Dr. Froines responded that they were the studies that formed the basis for the 1987 IARC recommendation and subsequent follow-up studies. Dr. Carpenter said the important point for him in supporting the nomination was that a causal relationship is credible. Dr. Zahm said she could not support listing because there is little distinction made in the IARC document about presence of asbestos. The vote on the motion was a tie with five yes votes (Carpenter, Froines, Kelsey, Moure-Eraso, Pelling) and five no votes (Bonney, Dragan, Medinsky, Smith, Zahm) with one abstention (Frederick) and therefore the motion did not pass. Dr. Frederick abstained from breaking the tie declaring that the message to the NTP that this was a split vote was the appropriate message. He asked whether any of those members who voted "no" did so because they favored listing as *known to be a human carcinogen*. None of the members felt it should be listed as a known human carcinogen and either felt that the nomination of talc, containing asbestiform fibers, not containing asbestos, should be deferred for development of further information or should not be listed in the RoC for other reasons such as uncertainty as to whether asbestos might be present, or the carcinogenic mechanisms may not be operating in humans. Dr. Medinsky moved that the nomination of talc, not containing asbestiform fibers not be listed in the 10th RoC. Dr. Pelling seconded the motion. Dr. Smith indicated that action should be deferred to allow further consideration of the ovarian cancer studies and information on the extent of contamination of the non-asbestiform talc in these studies. Dr. Froines

Summary Minutes - December 13-15, 2000

NTP Board of Scientific Counselors Report on Carcinogens Subcommittee

referred to the animal studies and opined that there were some questions pertaining to the species specificity of the overload issue and other related questions that need answering before rejecting the nomination. Dr. Medinsky's motion passed with seven yes votes to three no votes (Kelsey, Moure-Eraso, Smith). Dr. Smith said the ovarian cancer epidemiology studies have not been adequately examined, so he supported deferral. Dr. Moure-Eraso believed the ovarian cancer evidence was adequate to support listing as *reasonably anticipated to be a human carcinogen*. Dr. Kelsey also supported that listing. Dr. Froines asked that the NTP leadership communicate to the appropriate representatives at OSHA and MSHA that their regulatory standard of 5 mg/m³ is not an appropriate standard for talc.

Estrogens, Steroidal -- Dr. Kamel presented the nomination and said that steroidal estrogens were nominated by RG1 for listing in the 10th RoC as *known to be human carcinogens* based on IARC monographs published in 1987 and 1999, which identified steroidal estrogens and postmenopausal estrogen therapy as known human carcinogens. Estrogens are defined in terms of physiological effects with most effects involving the estrogen receptor and are endogenous hormones defined by the presence of the four-ring steroid nucleus. She said conjugated estrogens are listed in the 9th RoC as *known to be human carcinogens*, while two naturally occurring estrogens, estradiol and estrone, and two synthetic steroidal estrogens, ethinylestradiol and mestranol, are listed as *reasonably anticipated to be human carcinogens*. Dr. Kamel said that besides exposure as an endogenous hormone, humans are exposed through medical uses, environmental exposure, and occupational exposure in the pharmaceutical industry. Exposures considered in epidemiologic studies were estrogen replacement therapy, hormone replacement therapy (included estrogen and progestin combinations), and oral contraceptive use (typically estrogen and progestin). She reviewed the information presented in an 1999 IARC monograph review of hormonal contraception and postmenopausal hormonal therapy, primarily cohort and case-control studies looking at endometrial and breast cancer. For estrogen replacement therapy, three cohort and 30 case-control studies showed an increased risk for endometrial cancer which remained elevated after cessation of use. From 15 cohort and 23 case-control studies, there was shown to be a small increase in risk for breast cancer. For hormone replacement therapy, there was a slightly elevated risk for endometrial cancer but a risk for breast cancer similar to that for estrogen alone. For oral contraceptive use, based on over 50,000 cases, there was a small increase in risk for breast cancer that does not return to baseline until 10 years after cessation of use. For other types of cancers, there was either no change in risk or decreased risk with the exception of oral contraceptive use where some studies showed an increased risk for cervical or liver cancer. Dr. Kamel reported on NTP's review of studies published since the IARC monograph. Current studies of hormone/estrogen replacement therapy generally show increased risk for endometrial and breast cancer, and one case-control study with estrogen replacement therapy showed increased risk of ovarian clear cell tumors. Current studies of oral contraceptive use showed decreased or little change in risk for the three cancers. Dr. Kamel summarized the wealth of information on experimental animals reported by IARC which was considered sufficient evidence for estradiol, estrone, ethinylestradiol, and mestranol, and limited evidence for estriol and conjugated estrogens. IARC reviewed evidence of genotoxicity for animal cells *in vivo* and *in vitro*, and human cells *in vitro*, as did the NTP for more current studies. The *in vitro* studies showed evidence of aneuploidy, micronuclei and DNA damage, as well as chromosomal aberrations in human lymphocytes, while animal cells *in vivo* demonstrated some of the same changes. She said that possible carcinogenic mechanisms include proliferation of estrogen-responsive tissues, direct and indirect genotoxicity, and genetic susceptibility. Dr. Kamel reported that RG1 voted unanimously with seven votes, and RG2 voted unanimously with eight votes to recommend listing steroidal estrogens in the 10th RoC as *known to be human carcinogens*.

Public Comments: None.

Primary Reviews: Dr. Yamasaki, a primary reviewer, agreed with the proposed listing. He believed the data were sufficient for endometrial cancer and somewhat less so for breast cancer and estrogen replacement therapy. He discussed studies on molecular mechanisms for the neoplastic effects of

Summary Minutes - December 13-15, 2000

NTP Board of Scientific Counselors Report on Carcinogens Subcommittee

estrogen on the endometrium as being mediated through down-regulation of tumor suppressor genes, the connexins, and how progestin inhibits cell proliferation through expression of certain connexins.

Dr. Phillips, also a primary reviewer, agreed with the proposed listing. His concerns were that there needed to be some prominently placed modifying or balancing statements in the DBD about the benefits of the estrogens. He said there also needed to be made a stronger distinction between *in vivo* and *in vitro* studies on human toxicity.

Dr. Dragan, also a primary reviewer, had a problem with a inclusive labelling of estrogens, steroidal as *known to be human carcinogens*. She thought there were insufficient data to apply this label to all of the estrogens cited. For example, she commented that for estrone and estriol the human data are inadequate although the animal data are sufficient. Further, one has to consider the formulation and pattern of use.

There ensued a discussion on whether there was enough emphasis on the use or circumstances of use by women. Dr. Bucher said the definition used by the NTP was that steroidal estrogens had a steroidal structure and estrogenic activity through interaction with an estrogen receptor. He believed that the data on estrogen use alone in relation to endometrial cancer were very strong. He recognized that the combination therapies have a mediating effect but thought that could be handled with more emphasis in the actual listing. Dr. Frederick emphasized that like the issue with tamoxifen, the wording has to be carefully handled to deal with the positive as well as the negative aspects of its use. Dr. Smith commented that epidemiologists look at exposure scenarios and suggested that NTP might want to consider that approach more when working with human data. Dr. Zahm mentioned an NCI study wherein addition of progestin to estrogen resulted in an increased risk of breast cancer. Dr. Medinsky said that physicians rarely discuss the risks when they're prescribing hormone therapy and basically only talk about the benefits. Dr. Froines commented that this was in part an issue of the epidemiologic orientation versus the toxicological orientation. Dr. Frederick said that the process as it is set up is more agent oriented and we can't change that at present so we should have careful wording with regard to listing that focuses on the exposure scenario and the positive and negative aspects associated with it. Dr. Dragan again expressed concern that even though the data for estrogen replacement therapy are strong, the data for some of the individual estrogens are not, nor for their metabolites. Dr. Moure-Eraso asked about inclusion of diethylstilbestrol (DES), and Dr. Bucher said it was listed in the first *Report* and ever since as *known to be a human carcinogen*.

Dr. Dragan moved that the action of conjugated estrogens and 17 β -estradiol in postmenopausal women with an intact uterus be listed as carcinogenic. The motion died for lack of a second. Dr. Froines moved to recommend that estrogens, steroidal, be listed in the 10th RoC as *known to be human carcinogens*. Dr. Zahm seconded the motion, which was accepted with eight yes votes to one no vote (Dragan). Dr. Dragan said the estrogens and metabolites need to be specified. Dr. Kelsey was not present.

Wood Dust -- Dr. Scott Masten, NIEHS, presented the nomination and said that wood dust was nominated by OSHA for listing in the 10th RoC based on the 1995 IARC designation as carcinogenic to humans (Group 1). He said the IARC evaluation was based on sufficient evidence of an association between wood dust exposure and cancer in humans, primarily of the nasal cavities and paranasal sinuses. Dr. Masten reported that at least two million people are exposed occupationally to wood dust worldwide, and there is also widespread non-occupational exposure. Wood dust is a complex mixture which will vary with the types of wood used. With regard to studies of wood dust exposure and cancer in humans, Dr. Masten said the association between wood dust exposure and cancers of the nose were observed in numerous case reports, cohort studies, and case-control studies, which was true both for occupations associated with wood dust exposure and in studies where exposure was directly estimated. Risks were consistently high for a specific type of nasal cancer, sinonasal adenocarcinoma, especially in studies of European populations. For studies conducted in the U.S. and other parts of North America, lower but

Summary Minutes - December 13-15, 2000

NTP Board of Scientific Counselors Report on Carcinogens Subcommittee

significant excess risks were seen. Other types of cancers were seen in some but not all studies. As regards experimental carcinogenesis, he said there have been a few studies using animal models, but basically overall there is considered to be inadequate evidence for the carcinogenicity of wood dust in experimental animals. An increased frequency of DNA damage and micronuclei has been observed in occupationally exposed humans, while *in vitro* and *in vivo* tests in mammalian systems with solvent extracts of some wood dusts have shown positive results for DNA damage, micronucleus induction, and chromosomal aberrations. Among mechanistic considerations are that several chemical constituents of wood/wood dust are known to be mutagens and/or rodent carcinogens, and chronic exposure to wood dust in humans is associated with inflammatory reactions and reduced mucociliary clearance in the nasal cavity and metaplasia and dysplasia of the nasal epithelium. Dr. Masten reported that RG1 voted unanimously with eight votes and RG2 voted unanimously with seven votes to recommend listing wood dust in the 10th RoC as *known to be a human carcinogen*.

Public Comment: Dr. William Blot, International Epidemiology Institute, Ltd., representing the Inter-Industry Wood Dust Coordinating Committee, said he would briefly review the epidemiologic evidence relevant to wood dust carcinogenicity. He said there was clear evidence of an increased risk of nasal adenocarcinoma, but from studies in Europe, primarily of workers exposed in the furniture and cabinet making industries with most exposures occurring prior to World War II. Dr. Blot referred to the IARC working group which noted that the risks of nasal cancer were lower in the U.S. than in Europe. He then reviewed the American cohort and case-control studies and said the cohort studies do not show any evidence of increased risk of nasal cancer, while the case-control studies jump around with no clear pattern of an increased risk. Dr. Blot concluded that if the charge of the *Report on Carcinogens* is to protect American health then there is no basis for listing wood dust. Dr. Zahm inquired about a study by Brinton *et al.* for which he had shown overall results for nasal cancer, but not adenocarcinoma. Dr. Blot responded that there were two cell types, one with a reduced relative risk and one with a relative risk of 5.0 but no overall excess of nasal cancer. Dr. Medinsky asked for reasons for the much lower incidence of cancer in the U.S. Dr. Blot said no clear cut reasons had been uncovered. Dr. John Festa, American Paperboard Association, noted that the NTP had previously deferred action to consider worker exposure circumstances on the basis of disparities in geographical and other factors, focusing evaluation on the variables and conditions applicable to current U.S. workers, and cited the decision to defer action on boot and shoe manufacture. Dr. Frederick said the decision was to defer and there were too many differences between that proposal and this one to use as a basis for anything. Dr. Medinsky observed that part of the difficulty is that we're dealing with a complex substance rather than a discrete chemical.

Primary Reviews: Dr. Moure-Eraso, a primary reviewer, agreed with the proposed listing. He agreed that the cancer risk might be lower in U.S. than in European workers but lower does not mean an absence of exponential cancer effects in U.S. workers.

Dr. Kelsey, also a primary reviewer, was unable to be present so Dr. Mary Wolfe, NIEHS, read his comments into the record. Dr. Kelsey agreed with the proposed listing. He said that the most difficult portion of the evaluation of wood dust for listing involves an understanding of the complex nature of the exposure in question. Dr. Kelsey noted that although it has been suggested that the majority of the risk is restricted to Europe, there are positive studies that have been reported in North America.

Dr. Zahm, also a primary reviewer, agreed with the proposed listing. She agreed with Dr. Festa that the language of the *Report* is that it has to be agents or mixtures that are known or reasonably anticipated to cause cancer in humans and to which a significant number of people in the U.S. are exposed., and in her view both of these caveats are met. First, wood dust is a well established human carcinogen and U.S. populations have exposures to the same types of wood dusts linked to high risks of nasal cancer in European studies. Dr. Zahm said that the different exposure distribution patterns and levels may be responsible for the lower level of risk seen in the U.S. U.S. populations have demonstrated excess nasal

Summary Minutes - December 13-15, 2000

NTP Board of Scientific Counselors Report on Carcinogens Subcommittee

cancer risk associated with wood dust in several case-control studies, albeit often at lower levels than in European studies. Finally, confounding by formaldehyde and smoking are unlikely to explain the excesses.

Dr. Moure-Eraso moved to recommend that wood dust be listed in the 10th RoC as *known to be a human carcinogen*. Dr. Zahm seconded the motion, which was accepted unanimously with eight votes. (Dr. Froines served as acting chair while Dr. Frederick was temporarily absent from the room, and did not vote.)

Prepared by Dr. Larry Hart

May 7, 2001

AGENDA
NATIONAL TOXICOLOGY PROGRAM (NTP)
BOARD OF SCIENTIFIC COUNSELORS
REPORT ON CARCINOGENS (RoC) SUBCOMMITTEE MEETING

Wyndham City Center
The New Hampshire Ballroom
1143 New Hampshire Avenue, NW
Washington, DC

December 13	9:00 a.m.	Registration
	9:30 a.m.	Meeting begins
December 14-15	8:30 a.m.	Meeting begins

Review of Substances for Listing In or Delisting From the Tenth Report on Carcinogens

Nomination/Cas No.	Primary Reviewers	NIEHS Staff Presenter	To Be Reviewed For*
Broad Spectrum UV Radiation and UVA, UVB, and UVC	A. Smith J. Pelling H. Yamasaki	R. Lunn	Listing in the 10th Report
Trichloroethylene (TCE) 79-01-6	S. Zahm G. Bonney R. Moure-Eraso	J. Huff	Upgrade to Known to be a Human Carcinogen
Methyleugenol 93-15-2	M. Medinsky Y. Dragan G. Bonney	R. Melnick	Listing in the 10th Report
Metallic Nickel & Nickel Alloys	D. Phillips K. Kelsey J. Froines	M. Waalkes	Listing in the 10th Report
Chloramphenicol 56-75-7	J. Pelling A. Smith H. Carpenter	J. Haseman	Listing in the 10th Report
Talc (asbestiform and non- asbestiform) 14807-96-6	J. Froines H. Carpenter M. Medinsky	J. Huff (asbestiform) F. Kamel (non-asbestiform)	Listing in the 10th Report
Estrogens, steroidal	H. Yamasaki Y. Dragan D. Phillips	F. Kamel	Listing in the 10th Report

Wood Dust

R. Moure-Eraso
K. Kelsey
S. Zahm

S. Masten

Listing in the
10th Report

**ROSTER FOR THE
NATIONAL TOXICOLOGY PROGRAM
BOARD OF SCIENTIFIC COUNSELORS'
REPORT ON CARCINOGENS SUBCOMMITTEE MEETING
DECEMBER 13 - 15, 2000**

George Bonney, Ph.D.

Professor, Microbiology Director
Statistical Genetics and Bioinformatics Unit
National Human Genome Center at Howard
University
2216 Sixth Street, NW, Suite 205
Washington, DC 20059
(Genetic Epidemiology, Carcinogenesis,
Biostatistics)

Hillary M. Carpenter, III, Ph.D.

Toxicologist
Minnesota Department of Health
121 East Seventh Place, Suite 220
P.O. Box 64975
St. Paul, MN 55164-0975
(Toxicology, Risk Assessment, Public Health)

Yvonne P. Dragan, Ph.D.

Assistant Professor
Ohio State University, School of Public Health
1148 James Cancer Hospital & Research Institute
300 W 10th Avenue
Columbus, OH 43210
(Toxicology & Experimental Carcinogenesis)

Clay Frederick, Ph.D. (Chair)

Senior Research Fellow
Mechanistic Toxicology Group
Rohm and Haas Company
727 Norristown Road
Spring House, PA 19477
(Toxicology, Animal Models)

John R. Froines, Ph.D.

Professor and Director
UCLA Center for Occupational
and Environmental Health
UCLA School of Public Health
650 Charles E. Young Drive
Box 951772
Los Angeles, CA 90095-1772
(Occupational Health)

Stephen S. Hecht, Ph.D. *

Wallin Professor of Cancer Prevention
University of Minnesota Cancer Centers
Box 806 MAYO
420 Delaware Street, SE

Karl T. Kelsey, M.D.

Occupational Health Program
Harvard School of Public Health and Medical
School
665 Huntington Avenue
Boston, MA 02115
(Occupational and Molecular Epidemiology)

Michele Medinsky, Ph.D.

Toxicology Consultant
5505 Frenchmans Creek
Durham, NC 27713
(Metabolism, Toxicokinetics)

Rafael Moure-Eraso, Ph.D., C.I.H.

Associate Professor
Department of Work Environment
College of Engineering
University of Massachusetts Lowell
One University Avenue
Lowell, MA 01854
(Industrial Hygiene Worker Health)

Jill C. Pelling, Ph.D.

Professor
Dept of Pathology and Laboratory Medicine
University of Kansas Medical Center
3901 Rainbow Boulevard
Kansas City, KS 66160-7410
(Mechanisms of Carcinogenesis)

Walter W. Piegorsch, Ph.D. *

Professor of Statistics
Director of Undergraduate Studies
Department of Statistics
University of South Carolina
216 LeConte Building
Columbia, SC 29208
(Biostatistics, Risk Assessment)

Allan H. Smith, MD, Ph.D.

Professor of Epidemiology
School of Public Health
University of California, Berkeley
140 Warren Hall
Berkeley, CA 94720-7360
(Epidemiology)

**ROSTER FOR THE
NATIONAL TOXICOLOGY PROGRAM
BOARD OF SCIENTIFIC COUNSELORS'
REPORT ON CARCINOGENS SUBCOMMITTEE MEETING
DECEMBER 13 - 15, 2000**

*not attending

Shelia H. Zahm, Sc.D.

Deputy Director

Division of Cancer Epidemiology & Genetics

National Cancer Institute

6120 Executive Blvd., EPS 8074

Rockville, MD 20892-7242

Fed Ex: Rockville, MD 20852

(Cancer Epidemiology, with Focus on Exposures to
Chemical Hazards)

Ad Hoc Consultants

David H. Phillips, Ph.D., DSc, FRCPath

Research Scientist, Institute of Cancer Research

Haddow Laboratories

Cotswold Road

Sutton SM2 5NG, ENGLAND

(Molecular Epidemiology, Carcinogenesis)

Hiroshi Yamasaki, Ph.D.

Professor, Faculty of Science

Kwansei Gakuin University

1-1-115 Uegahara, Nishonomiya

622 JAPAN

(Experimental Carcinogenesis)